EVIDENCE-BASED MEDICINE METHODOLOGY – SYSTEMATIC REVIEWS AND META-ANALYSES

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Meta-analysis was first proposed by Glass (1976). The term meta-analysis refers to the statistical methods to systematically combine the outcomes of a series of different experiments or investigations. Over 30 years of application and development, meta-analysis has been established as a useful method in summarizing research evidence for clinical decision-making. Consequently, it becomes a major foundation for Evidence-Based Medicine. Meta-analysis is also referred as *quantitative review* (Greenland 1987) or systematic *review* (Peto 1987). The latter denotes a full range of systematic assessment of clinical evidence, not necessarily including statistical synthesis of evidence. The contribution of meta-analysis in the management of osteoarthritis is apparent, from the confirmation of the treatment effects for exercise (Roddy 2005), to the comparative effectiveness between acetaminophen and NSAIDs (Zhang 2004), as well as the gastrointestinal toxicity of NSAIDs (Ofman 2002) and more recently the cardiovascular side effects of rofecoxib (Juni 2004). It also raises questions such as whether topical NSAIDs only work for OA in short-term period (Lin 2004), and whether vascular side effects are the class effects of COX-2 inhibitors or NSAIDs (Kearney 2006).
Whilst the merits of meta-analysis are recognized, it has some pitfalls including publication bias and problems with heterogeneity. It is debated, for example, whether an overall pooling of effect sizes of glucosamine from different trials irrespective of quality would be adequate (Towheed 2005). Nevertheless, like many other developments, meta-analysis continues to evolve and contribute to the field. It has become a major tool in the development of treatment guidelines (Zhang 2005, 2007) and has been extended to answer other clinical questions such as diagnosis (Zhang 2006).
References will be provided upon request.

ANGIOGENESIS IN OA

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Purpose: To explain the relevance of inflammatory blood vessel growth in OA
Methods: Synthesis of recent and historical data
Results: During OA, new blood vessels grow in synovium, at the osteochondral junction and in osteophytes. Neovascularisation can facilitate inflammation, degrade cartilage matrix, and lead to new bone formation and sensory nerve growth. Different factors appear to drive neovascularisation in different joint structures. Inflammation, both in the synovium and within the subchondral bone, stimulates angiogenesis by tipping the balance between angiogenic and anti-angiogenic factors.
Conclusions: Addressing angiogenesis and the factors that drive it, offers the potential to modify both symptoms and structural progression in OA.

CHEMOKINES IN OA

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Purpose: Chemokines represent a large family of small molecules with conserved structural motifs which act on 7 transmembrane receptors. The aim of our work was to investigate on the major effects mediated by these molecules on cartilage, bone and synovium in Osteoarthritis.
Methods: Primary human chondrocytes and osteoblasts and full thickness cartilage or bone samples were obtained from OA patients undergoing joint arthroplasty. High density or three dimensional or organ culture, RNA (real time PCR and microarray) and protein (immunohistochemistry, ELISA or fluorescence bead-based multiplex assays) expression analysis, enzyme activity assays, primary human monocytes chemotaxis assays and functional genomic analysis were employed in our studies.
Results: Some chemokines are constitutively expressed in normal chondrocytes and strongly unregulated in OA (Borzi RM et al, FEBS Lett 1999; 455:238). The analysis of the distribution of the chemokine receptors indicates their expression in the middle lower layers of the tissue. Chemokine activation is able to induce DNA synthesis and gene expression and release of MMPs (MMP-1, MMP-3 and MMP-13) and of other enzymes with key roles in ECM breakdown, such as NAG, cathepsin B and aggrecanases (Borzi RM et al, Arthritis Rheum 2000;43:1734; Mazzetti I et al, Arthritis Rheum 2004;50:112).GROα/CXCL1 induces chondrocyte apoptosis in chondrocytes cultured in vitro or in the context of their native ECM (Borzi RM et al, Arthritis Rheum 2002;46:3201).This feature is in keeping with the ability reported for GROα/CXCL1 and IL-8/CXCL8 to promote chondrocyte hypertrophy thus pushing the chondrocytes beyond the status of "maturational arrest" in chondrogenesis, kept in normal healthy cartilage. Noteworthy, GROα/CXCL1 induced chondrocyte hypertrophy requires a co-receptor role of chondroitin-sulphate and is inhibited by soluble CS possibly via a scavenging activity (Olivotto E et al, J Cell Physiol 2007; 210: 417).
Chemokines can also affect the underlying bone contributing to the thickening which takes place in OA. IP-10/CXCL10 and BCA-1/CXCL13 up regulates gene expression of alkaline phosphatase and collagen type I and also alkaline phosphatase activity (Lisignoli G et al, J Cell Physiol 2006; 206:78-85) in osteoblasts derived from OA patients. With regards to chemokine effects on the synovium, chemokines may likely contribute to the recruitment of inflammatory cells into the synovial membrane and into the synovial fluid. Recent experiments with primary human monocytes (previously shown to be the prevalent cell type in OA synovial fluid) revealed that MCP-1 is the chemokine most closely associated with in vitro chemotaxis, and that it is dependent on both NF-κB activating kinases.
Conclusions: Chemokines contribute to cartilage pathophysiology through autocrine and paracrine loops and mediate a crosstalk among the joint compartments. Since many chemokines are produced by normal chondrocytes, a detailed gene expression analysis of chemokines and receptors in normal and OA cartilage as well as in chondrocyte differentiation or endochondral ossification could help to distinguish members of this family with physiological functions from chemokines that deserve to be targeted for therapeutic intervention.
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EVOLVING INDICATIONS FOR JOINT REPLACEMENT SURGERY IN OA: HIP, KNEE AND ANKLE

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Purpose: Total joint arthroplasty has become a reproducible surgical treatment for osteoarthritis with excellent outcomes. In 2003 approximately 418,000 total knee replacements and over 220,000 hip replacements were performed in the U.S. and this number is increasing at a rate of 11% for knee replacement and 2.5% for hip replacement per year. During the last decade the indications for both of these procedures has widened.
Methods: Previously younger and very elderly patients with OA were discouraged from having total hip or knee replace-

ment because of the increased incidence of failures in those patients. The primary reasons for the failures observed were wear, loosening and mechanical failures. Recent advances in designs, materials, surgical technique and instrumentation has dramatically improved these procedures. For example, alternative bearing surfaces such as highly crossed linked polyethylene and enhanced fixation methods using improved porous surfaced implants have significantly reduced wear, bone loss from osteolysis and implant loosening. Minimally invasive surgical procedures have accelerated the rehabilitation of patients and sophisticated instrumentation provides excellent restoration of anatomy.

Results: Using these contemporary design materials and surgical techniques implant survival rates of 98-99% at ten years and 90-95% at 15-20 years can be expected following total hip or knee replacement even in younger, active patients. By contrast, total ankle replacement was until recently a procedure of historical interest because of the high rate of loosening and mechanical failure. Early results of total ankle replacement with contemporary designs have been encouraging, but current recommendations are for the procedure to be performed for low demand patients by surgeons who have completed special training for the technique.

Conclusions: Future improvement in designs and materials of joint replacements will continue to enhance patient outcomes and functional long-term implant survival.

SHOULDER ARTHROPLASTY FOR ARTHRITIS – SURFACE, STEMMED OR REVERSE

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Shoulder replacement using an ivory prosthesis was first recorded in 1890 by a Romanian surgeon Theristocles Gluck who was born in 1853. However, Emile Pean is more widely recognized for a shoulder replacement, made of rubber and platinum, he performed in Paris in 1893 to treat the late effects of tuberculosis.

Despite these early pioneering operations it was not until the 1950s that significant advances were made in shoulder arthroplasty, which is currently used today in the treatment of osteoarthritis, rheumatoid arthritis, cuff tear arthropathy, osteonecrosis, instability arthritis and post infective arthropathy.

In Europe in the 1950s tumour prostheses were developed to replace the resected proximal humerus, but as the rotator cuff was usually sacrificed during these procedures this resulted in anterosuperior subluxation of the implant. Constrained joints like hip replacements were therefore developed to stabilize the articulation, but these lateralized the centre of rotation of the shoulder resulting in early loosening. Reversing the ball and socket geometry, i.e. with the ball on the glenoid and the socket on the humerus, was attempted in a variety of designs, but all failed because the centre of rotation remained lateral to the scapula. This resulted in limitation of movement and considerable torque being transmitted to the glenoid component causing loosening. In the 1970s Paul Grammont redesigned the reverse geometry prosthesis (Delta) for the use in cuff arthropathy. He used a large glenoid hemisphere with no neck and a socket on the humeral side which inclined almost horizontally and covered less than half of the hemisphere. This design medialises the centre of rotation and therefore minimises the torque transmitted to the glenoid component. This implant allows, in the absence of the cuff, the anterior and posterior deltoid fibres to act as abductors of the shoulder. It also restores the tension in the deltoid by lowering the humerus with respect to the acromion, thus allowing the deltoid to function without the rotator cuff. Although this can therefore restore active elevation rotation still remains limited. The results of this implant in the treatment of rotator cuff arthropathy are a significant improvement on the alternatives available at 5 - 10 years although it is still recommended for older patients (over 70 years) with low functional demands. It has also been used in rheumatoid arthritis, where cuff function is often poor, in revision surgery, in tumour surgery and to treat difficult proximal humeral fractures, all of which have far less predictable results.

Charles Neer working in the 1950s in New York developed proximal humeral head prosthesis for the management of fractures, but later in 1972 developed a glenoid component so that glenohumeral arthritis could be treated by total shoulder replacement. The Neer humeral prosthesis was a cemented monoblock design, but as with hip arthroplasty modular designs were developed to allow various stem/head combinations to be used. In the 1990s, with the recognition of the anatomical variation of the proximal humerus, particularly with respect of offset and version of the humeral head to the humeral shaft, third generation modular prostheses have been developed. These allow the surgeon to replicate the patients' proximal humeral anatomy using these stemmed implants which were also developed in uncemented forms. There are now many papers reporting the results of stemmed total shoulder and hemiarthroplasties in the treatment of both inflammatory and degenerative disease.

Surface replacement of the humeral head was developed initially in the late 1970s both in cemented and uncemented forms. These types of implants can be used in glenohumeral arthritis including osteonecrosis providing there is sufficient humeral head remaining - about 60% of normal is required. Such implants have advantages over stemmed prostheses whilst reported results for osteoarthritis, rheumatoid arthritis and osteonecrosis are certainly equivalent. Humeral implants can be reliably centered on the patients' humeral head and therefore negate the problems of variable inclination, version and posterior offset. Surface replacement requires minimal bone resection which is particularly important in the younger patient. Stems produce a stress riser at the tip of the prosthesis which may result in periprostheic fracture. 30% of unsatisfactory results post stemmed shoulder replacements are due to component malalignment, which could be prevented by the use of surface arthroplasty. Revision surgery for component malposition or for infection is very difficult both when the stem is cemented and uncemented as stem extraction can be very destructive to the proximal humerus. If complications occur requiring revision then certainly revising a surface replacement is much less demanding.

One of the most debated topics in shoulder surgery is whether to do a hemiarthroplasty or total replacement. There are advocates for both. With stemmed implants there seems to be an advantage in osteoarthritis for total replacement as the early pain relief and function is improved and the revision rate from hemi to total for glenoid erosion exceeds the rate of glenoid component revision. This is not true in surface replacement where results of hemi and total are comparable in osteoarthritis and rheumatoid. The rationale for a hemiarthroplasty is to avoid the insertion of polyethylene, which if worn produces debris which in turn causes the eventual loosening and failure of the joint. This is also the reported cause of failure in the reversed geometry Delta prosthesis where impingement of the humeral component on the scapula neck produces notching and wear of the polyethylene. The problem of polyethylene debris has led some to recommend drilling the glenoid surface to encourage fibrocartilage formation and others to use biolological resurfacing.

In conclusion there is now a choice of prostheses designed to manage particular pathologies. A stemmed prosthesis is required for fracture reconstruction as it was initially designed. A reverse prosthesis in cuff arthropathy, for which it was designed, will in an elderly individual achieve a better functional result than the alternative stemmed or surface implant. When the pathology is confined to the articular surface it would therefore appear rational to use a surface replacement as it was specifically designed for the use in arthritis. The problem of the glenoid and potential